--23. **(New)** A method for detecting antibodies present in sera from patients with rheumatoid arthritis, comprising:

a) contacting a biological sample to be analyzed for the presence of said antibodies with a peptide of claim 1, and

b) detecting the immunological complex formed between said antibodies and said peptide.

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24. **(New)** The peptide of claim 7 which has the primary amino acid structure:
8 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 4).

25. **(New)** The peptide of claim 8, wherein the amino acids flanking the citrulline residue have a small volume.

26. **(New)** The peptide of claim 8 wherein the amino acids flanking the citrulline residue are selected from the group consisting of glycine, alanine, and serine.

27. **(New)**The peptide of claim 9 which comprises the amino acid sequence
QDTIHGHPCSXXGCRPGY (SEQ ID NO: 12).--

REMARKS

I. Status of the claims:

Claims 10, 11, 16, 17, 19, 21, and 22 are cancelled.

Claims 1, 8, 12, 13, 15, 18, and 20 are amended and new claims 23-27 are added.

Claims 1-9, 12-15, 18, 20, and 23-27 are currently pending.

II. Rationale and support for the amendment

Claims 10, 11, 16, and 17 are cancelled as being directed to a non-elected invention. Claims 21 and 22 are cancelled so as to facilitate the prosecution of the allowance of the instantly pending claims. Applicant expressly reserves the right to pursue the cancelled material in one or more continuation or divisional application. For the Examiner's convenience, a complete copy of all pending claims, including marked-up versions of the amended claims is attached.

III. Rejection under 35 U.S.C. §112

A. Claims 1-9, 12-15, and 18-22 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which is not described in the specification in such a way as to enable an artisan of ordinary skill to make and/or use the invention. The Examiner specifically recites that:

> [t]he specification does not disclose how to use the claimed peptide comprising SEQ ID NO:4 or SEQ ID NO:12, composition [sic] thereof and immunotoxin or kits comprising the said peptide for diagnosis or treatment of autoimmune diseases including rheumatoid arthritis. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass peptides that are not specifically recognized by autoimmune antibodies from patients suffering from rheumatoid arthritis (RA) or other autoimmune diseases.

Applicant respectfully traverses.

Firstly, rejection of claims 19, 21, and 22 is moot as these claims are cancelled by the instant Amendment.

Applicant asserts that one of ordinary skill in the art would recognize that the examined claims were directed to peptides which were *specifically* recognized by autoantibodies specific for rheumatoid arthritis (RA). Nevertheless, in order to make this clear, claim 1 is now amended to recite "*peptide is specifically recognised by rheumatoid arthritis autoimmune antibodies.*" This makes it clear that the claimed peptides are those recognised by antibodies that are specific to RA.

Applicant notes, that as currently amended the claims are limited to peptides as described above and to kits or diagnostics for diagnosing RA. Nevertheless, Applicant specifically reserves the right to pursue claims to the treatment RA and other autoimmune diseases and to the diagnosis of other autoimmune diseases in one or more divisional or continuation applications.

The Examiner also alleges, *inter alia*, that the "specification does not disclose...diagnosing patients with rheumatoid arthritis . . . ." Citing Jaarsveld *et al.* (*Clin. Exp. Rheum.* 1999, 17:689-697) and Schellekens *et al.* (*Arthritis & Rheum.*, 2000, 43:155-163), the Examiner asserts that

> there is a high level of unpredictability in diagnosing and treating subjects with autoimmune diseases including rheumatoid arthritis using the claimed citrullinated peptides and Applicant does not provide direction or guidance to do so. There is insufficient guidance in the specification as to how to use the instant invention.

See Office Action, page 4. Applicant responds as follows.

Applicant notes that the Specification at page 4, last paragraph, recites, in pertinent part, that "there is a need for diagnostic tools which make a very sensitive diagnosis of RA at a high specificity level possible." This is precisely the need which the instant invention meets.

Applicants have identified characteristics which have enabled Applicant to design and construct peptides which are more specifically recognized by RA specific antibodies. As noted in the Specification, on page 25 and the following pages, the peptides of the instant invention can be used in a diagnostic kit (with any one of several formats). Additionally, Applicant asserts that the peptides of the present invention may be employed in virtually any assay format that employs a known antigen (*e.g.* the presently claimed peptides) to detect antibodies that characterize a specific disease, RA in the instant case.

Applicant argues that one of ordinary skill in the art would be fully conversant with such diagnostic kits and assays. As recited in the Specification, last paragraph of p. 26, "[d]esign of immunoassays is subject to a great deal of variation, and many formats are known in the art." It is therefore clear that there is no need for the Specification to recite specific directions. As the Board of Patent Appeals and Interferences has pointed out that "[i]n satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well-known in the art . . . ." *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (B.P.A.I. 1992). In view of this fact it is

clear that there is no need for the specific recitation of directions for how to carry out the assays to diagnose RA.

Furthermore, no undue experimentation is necessary in order to use the presently claimed invention given that the nature of the claimed peptides is clearly set out and claimed. Specifically, the peptides of the instant invention mimic the immunogenic determinants of self-proteins recognized by RA-specific antibodies in the sera from patients with RA. The features identified by Applicant, as claimed in currently pending claim 1 include: a "peptide turn" comprising at least one citrulline (see also page 33, lines10-18 which discuss the import of this feature), two cysteine residues separated by less than 12 amino acids with the citrulline, residue, which is part of the peptide turn being one of the residues, and the peptide must be specifically recognized by antibodies which are specific for RA.

As is demonstrated by Example 3 in the specification these currently claimed peptides can be used for used for a more convenient and sensitive diagnosis using any assay well known in the art (*see*, Specification beginning at page 34). Example 3 shows a comparison of analysis using peptides according to the instant invention compared with previously known peptides and reference test systems. As demonstrated by the data presented in Example 3 the peptides of the present invention provide specificity which is surprisingly superior to the results obtained using previously known peptides. Furthermore, Example 4 (beginning on page 38 of the Specification) reports the results of assays using a combination of two antigens lines to diagnose RA. As noted at page 41, the tests using the claimed peptides have "a high specificity and thus a high PPV [positive predictive value], and shows clear complementarity to RF [rheumatoid factors]. As it can replace AKA [anti-keratin antibodies] testing, it is a valuable tool in the differential diagnosis of RA."

From the results reported in Examples 3 and 4 it is clear that if similar tests were performed on the sera of patients with previously undiagnosed RA, the skilled artisan would be able to differential between the presence of RA versus other diseases. Thus, even if the Examiner's assertion regarding the unpredictability of RA diagnosis were previously true, Applicant has provided sufficient data to demonstrate the efficacy of the presently claimed peptides. Applicant asserts that this data meets the enablement requirements of 35 U.S.C. §112, first paragraph.

Therefore, Applicant believes that the Examiner's assertion, *supra*, "there is a high level of unpredictability in diagnosing and treating subjects with auto immune diseases including rheumatoid arthritis using the claimed citrullinated peptides . . ." (emphasis added), is contrary to the weight of the evidence on the record. First, Examiner's citation to Jaarsveld *et al.* and Schellelkens *et al.* which do not report the use of the currently claimed peptides provides no evidence that it would be difficult to diagnose RA using the currently claimed peptides, as these references do not teach or suggest use of the claimed peptides. Second, as noted above, Applicant has provided, in the instant Specification undisputed proof of the predictive value of tests using the presently claimed peptides.

Finally, in further support of Applicant's position, submitted herewith as part of a Supplemental Information Disclosure Statement are copies of four recent references which support Applicant's position (all references are from *Arthritis and Rheumatism*, vol. 46, 2002). For example Burlingame *et al.* (p. S541) demonstrate that anti-CCP (cyclic citrullinated peptides) antibodies are a very useful diagnostic marker for RA, showing specificity of 99%. The Dahlqvist *et al.* (p. S200) reference shows that the presence of anti-CCP antibodies in patients previously undiagnosed with RA, predicts, in a statistically significant manner, the

development of RA more than a year before the onset of symptoms. The findings of Dahlqvist *et al.* are supported by Nielsen *et al.* (p. S370) which reports the presence of autoantibodies, including anti-CCP antibodies, in the sera of at least 47% of patients who develop RA in one to six year. Finally, the Suzuki *et al.* (p. S543) also confirms that antibodies to CCP are especially useful serological markers for the diagnosis of RA.

The Examiner recites that "with respect to radiological damage scores the combination of RF and APF is a better prognostic marker than the single test alone . . . ." Applicant contends that whether or not this is true is irrelevant to the present discussion. In order for a diagnostician to be able to combined markers, efficient markers must first be developed. The currently claimed peptides and kits provide the necessary means for precisely this type of efficient markers.

In summary, Applicant contends that the currently claimed peptides and kits are sufficiently described in the specification so as to enable one of ordinary skill in the art would be able to use them diagnose RA in a manner which was more specific and efficient than with any peptides known in the prior art. In view of the discussion above, and absent evidence to the contrary of that presented in the Specification at Examples 3 and 4, Applicant believes that the current rejection of the claims under 35 U.S.C. §112, first paragraph has been overcome and should be withdrawn.

B. Claims 8 and 12 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Claim 12 is rejected for its use of the phrase "such as." In response to this rejection claim 12 is amended to remove the offending phrase. Accordingly, Applicant believes that the rejection of claim 12 under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

C. Claim 8 is rejected as allegedly being indefinite for its use of the phrase "small volume." The Examiner alleges that it is not clear what the metes and bounds of this limitation are. Applicant respectfully traverses. Firstly, the offending phrase is removed from the currently pending claim 8. Consequently, Applicant contends that the rejection of claim 8 has been overcome.

However, the limitation "small volume" is added as part of new dependent claim 25. Therefore, Applicant traverses the rejection as follows. Applicant refers the Examiner to page 14, lines 20-24 of the Specification which provides examples of amino acids having as "small volume," specifically glycine and serine. Furthermore, Applicant contends that one of ordinary skill in the art would know that a measure of an amino acid's volume is SAA (*i.e.*, solvent accessible area). For Gly, Ala, and Ser the SAA values are 88.534 $Å^2$, 106.964 $Å^2$, and 115.932 $Å^2$, respectively. These values were calculated using commercially available software.[1] It is Applicant's assertion that an artisan of ordinary skill at the time the application was filed would clearly understand what is meant by "small volume" and the use of this term is therefore definite within the meaning of 35 U.S.C. §112, second paragraph.

Since the SAA-value for alanine is between the values for glycine and serine, it is clear that at least alanine would also be considered a "small" amino acid. Furthermore, the language of the claim is such that "small" is also clearly defined by context (*i.e.* the amino acids do not interact with the citrulline side chain. In view of the foregoing, Applicant contends that one of ordinary skill in the art would find the meaning of the term "small volume" as used in the claims, to be clear and definite. Therefore, Applicant respectively requests that the rejection of claim 8

[1] The particular software used is known as InsightII and Discover (using the method of Connolly). The programs are available from Molecular Simulations Inc. (Parc Club Orsay Université, 20 Rue Jean Rostand, 91893, Orsay, FRANCE

be withdrawn and that claim 25 be found to comply with 35 U.S.C. §112, second paragraph, with respect to the term "small volume."

IV. Objection under 37 C.F.R. § 1.175(c)

Claims 13-15, 19, and 20 are objected to as allegedly being improper multiply dependent claims as being multiply dependent claims which depend from multiply dependent claims. Applicant respectfully traverses.

37 C.F.R. § 1.75(c) recites, in pertinent part, that "[a]ny dependent claim which refers to more than one other claim ("multiple dependent claim") shall refer to such other claims in the alternative only."

First, claim 19 is cancelled and objection to this claim is, therefore, moot. Furthermore, claims 13-15 and 20 now refer to only one claim each. Consequently, they cannot be considered improper multiple dependent claims. Accordingly, Applicant respectfully requests that the objection to these claims be withdrawn.

V. Rejection under 35 U.S.C. §102

Claim 1, 2, 4, 5, 8, 12, 15, 19, 20, and 22 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by WO 98/43660 as evidenced by U.S. Pat. No. 5,994,379. The Examiner alleges that WO 98/43660

> teaches a synthetic cyclic peptide comprising a sequence of less than 50 amino acid residues containing at least one citrulline residue between 2 cysteine residues spaced 4 amino acid residues apart, with the amino acid residues flanking said citrulline residue having small volume, and pharmaceutical composition thereof for nasal and oral administration....WO 98/43660 further teaches that said peptide can be used to treat irritable bowel syndrome.
>
> Evidentiary reference U.S. 5,994,379 discloses that irritable bowel syndrome is an autoimmune disease. . . .

See Office Action page 5. Applicant respectfully traverses.

Regarding the requirements to sustain a rejection for anticipation the Court of Appeals for the Federal Circuit has held that:

> For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art. *See in re Spada*, 911 F.2d 705, 708, 15 USPQ 2d 1655, 1657 (Fed. Cir. 1990). ("[T]he [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." (citations omitted)). Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that art not there.

Motorola, Inc. v. Interdigital Technology Corp., 43 USPQ 2d 1481, 1490 (Fed. Cir. 1997) (emphasis added).

First, Applicant notes that, as amended, the claims are no longer directed to methods of treating autoimmune disease. Rather, the instantly pending claims are directed to peptides which are specifically recognized by RA specific autoantibodies and to kits for detecting rheumatoid arthritis. Consequently, whether or not the reference teaches the treatment of autoimmune disease is moot, it does not teach diagnosis of RA, especially not using the currently claimed peptides. Second, as currently amended the current claims are directed to peptides having a minimum length of 14 amino acids. The basis for this limitation is found in the Specification at page 10, lines 9-15 and from the specific peptide sequences provided in Table 1 on page 12. In contrast the WO 98/43660 only describes a peptide having nine amino acids. Therefore, the WO 98/43660 reference does not anticipate the current claims because it does not teach a peptide of at least 14 amino acids. In view of the amendment and the foregoing arguments, Applicant contends that the rejection of the claims under 35 U.S.C. §102(a) has been overcome and should be withdrawn.

VI. Rejection under 35 U.S.C. §103

Claims 1-6, 8, 12-15, and 18-22 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over WO 99/28344 in view of Jaarsveld *et al.* (*Clin. Exp. Rheum.* 17:689-697, 1999). The Examiner asserts that WO 99/28344

> Teaches circularized peptides (i.e., cyclic) containing less than 50 amino acid residues and containing at least one citrulline residue and which react with antibodies from patients with rheumatoid arthritis (RA). WO 99/28344 further teaches pharmaceutical compositions comprising the peptides for therapy or diagnosis, i.e., medicaments for treatment or a diagnosticum for rheumatoid arthritis...wherein the peptides are attached to specific locations on solid substrate....
>
> WO 99/28344 does not teach at least one citrulline residue is present between two cysteine residues and that there are less than 12 amino acids residues between cysteine residues.
>
> Jaarsveld et al. teach an [sic] citrullinated cyclic peptide that was cyclized by substituting cysterine [sic]....
>
> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted cysteine for serine in a peptide taught by WO 99/28344 such as the peptides in claim 3 as taught by WO 99/28344 and to produce a cyclic peptide as taught by Jaarsveld et al. and WO 99/28344.
>
> One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to cyclize the peptide as taught by Jaarsveld...because WO 99/28344 teaches the advantage of cyclizing the peptides for conformational stability.

See Office Action pages 6 and 7. Applicant respectfully traverses.

The MPEP provides the following criteria which must be met in order to establish obviousness.

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable

> expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added).

MPEP 706.02(j) (emphasis added).

Applicant asserts that none of these criteria are met by the current rejection. Taking the *Vaeck* criteria in reverse order, Applicant first asserts that there is nothing in the combination of the cited references which teaches or suggests the claimed peptides. As the Examiner noted, the WO 99/28344 reference does not teach that at least one citrulline residue is present between two cysteine residues, nor does it teach that there are less than 12 amino acids between the two cysteine. Applicant contends that neither of the cited reference, either alone or in combination teach or suggest these limitations. Furthermore, the combination of the cited references taken in combination do not teach or suggest that the citrulline residue must reside within a "peptide turn" (*see* the Specification, p. 8, lines 4-11 and Figure 1 for a description of "peptide turn"). There is no teaching in the combination of the cited art regarding the importance of this limitation. Instead, the Jaarsveld *et al.* reference appears to be cited merely to teach peptide cyclization. Merely cyclizing the peptides described by the WO 99/28344 using the methods described by Jaarsveld *et al.* would not lead to the production of the instantly claimed peptides. Furthermore, such combination does not teach or suggest the claimed limitations. Thus, the combination of the cited references does not meet the third requirement of *Vaeck*.

With respect to the second step of *Vaeck*, there is nothing provided by the combination of the cited art that teaches or suggests benefit of that the presently claimed peptides or that such peptides could be successfully used as part of a kit which would provide a surprisingly good means to aid in the diagnosis of RA. Consequently, Applicant asserts that the combination of the cited references does not provide a reasonable expectation for the success of the claims directed to diagnostic kits.

Finally, with respect to the first criteria of *Vaeck*, there is nothing in the combination of the cited references or in the general knowledge of the artisan of ordinary skill which teaches or suggest combining the cited references so as to produce the currently claimed invention. There is no teaching or suggestion that merely cyclizing the peptides described in the WO 99/28344 reference using the methods described by Jaarsveld *et al.* would produce the presently claimed invention. It is only the data, results, and analyses first disclosed in the instant Specification that provide the necessary information and motivation to produce the currently claimed invention. Therefore the combination of the cited art fails to meet the first requirement of *Vaeck*.

In view of the foregoing it is Applicants assertion that the combination of the cited art fails to meet any of the requirements set out in *Vaeck*. Accordingly, Applicant believes that the rejection of the claims under 35 U.S.C. §103(a) has been overcome and should be withdrawn.

VII. Conclusion

In view of the foregoing, Applicant believes that all rejections of and objections to the claims and/or Specification have been overcome. Consequently, Applicant, respectfully requests that the Examiner reconsider the instant Application and issue a "Notice of Allowance" therefor.

The Examiner is invited to contact the undersigned patent agent at (713) 787-1589 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Matthew Madsen

Matthew L. Madsen
Reg. No. 45,594
Agent for Assignee
INNOGENETICS N.V.

HOWREY SIMON ARNOLD & WHITE, LLP
750 Bering Drive
Houston, Texas 77057-2198
(713) 787-1400

Date: November 27, 2002

AMENDMENT OF THE SPECIFICATION:

The paragraph at page 6, lines 24 and 25 is amended as follows:

Fig. 3 A-D: Reactivity on LIA of the cyclic and linear forms of four synthetic peptides ([a]A: IGP1611, [b]B: IGP1646, [c]C: IGP1650, [d]D: IGP1651).

PENDING CLAIMS:

1. **(Amended)** A peptide comprising a sequence of [less than] 14-50 amino acids characterised in that
   - it contains a peptide turn comprising at least one citrulline residue, and
   - it contains less than 12 amino acids between two cysteine residues, with said citrulline residue being one of the amino acids between said cysteine residues and
   - said peptide is specifically recognised by rheumatoid arthritis autoimmune antibodies from patients suffering from rheumatoid arthritis.

2. A peptide according to claim 1 characterised in that said peptide is a cyclic peptide.

3. (Amended) A peptide according to claim 1 characterised in that said peptide is biotinylated.

4. (Amended) A peptide according to claim 1 characterised in that said peptide is a synthetic peptide.

5. (Amended) A peptide according to claim 1 characterised in that said peptide contains 4 or 6 residues between the cysteine residues.

6. (Amended) A peptide according to claim 1 characterised in that said peptide has a sequence containing 14, 15, 16, 17 or 18 amino acids.

7. (Amended) A peptide according to claim 1 characterised in that said peptide has one of the following primary amino acid structures:

   8 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 1) or

   5 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 2) or

   4 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 3) or

   8 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 4) or

   6 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 5) or

   4 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 6).

8. **(Twice Amended)** A peptide according to claim 1 characterised in that the amino acids flanking the citrulline residue ~~[have a small volume and that they]~~ do not interact with the citrulline side chain.

9. (Amended) A peptide according to claim 1 comprising the amino acid sequence
QDTIHGHPCSXXGHRCGY (SEQ ID NO: 7), or
QDTIHGHPCSSXGHRCGY (SEQ ID NO: 8), or
QDTIHGHPCSXXGHQCGY (SEQ ID NO: 9), or
QDTIHGHPCSXXGHRCGQ (SEQ ID NO: 10), or
QDTIHGHPCSXXGHQCGQ (SEQ ID NO: 11), or
QDTIHGHPCSXXGCRPGY (SEQ ID NO: 12), or
HGHPCSXXGHRCGY (SEQ ID NO: 13), or
HGHPCSXXGCRPGY (SEQ ID NO: 14), or
HGHGCDXXGHRCGQ (SEQ ID NO: 15), or
HGHGCDSXGHRCGQ (SEQ ID NO: 16), or
QDTIVGWGCDSXGCRPGQ (SEQ ID NO: 17), or
VGWGCDSXGCRPGQ (SEQ ID NO: 18).

12. **(Twice Amended)** A diagnostic kit for use in detecting ~~[auto-immune diseases such as]~~ rheumatoid arthritis, said kit comprising at least one peptide according to claim 1, ~~[or an antibody according to claim 10,]~~ with said peptide or antibody optionally bound to a solid support.

13. **(Twice Amended)** A diagnostic kit according to claim 12, said kit comprising a range of peptides according to claim 1 ~~[or of antibodies according to claim 10]~~, optionally in combination with antigens that constitute immunogenic determinants for other auto-immune diseases, wherein said peptides are attached to specific locations on a solid substrate.

14. (Amended) A diagnostic kit according to claim 13, wherein said solid support is a membrane strip.

15. **(Twice Amended)** A diagnostic kit according to claim 13 ~~[wherein]~~ further comprising certain peptides that are not specific recognised by antibodies specific for rheumatoid arthritis and that are not attached to a solid support but are provided in the binding solution to be used as competitors and/or to block other antibodies that are present in sera from patients with autoimmune disease other than rheumatoid arthritis, thereby decreasing or eliminating possible cross-reaction and/or a-specific binding.

18. **(Twice Amended)** An immunotoxin molecule comprising a cell recognition molecule being a peptide of claim 1, ~~[or an antibody according to claim 10,]~~ covalently bound to a toxin molecule or active fragment thereof.

20. **(Twice Amended)** A diagnosticum for rheumatoid arthritis comprising a peptide according to claim 1 ~~[or an antibody according to claim 10]~~ or an immunotoxin molecule according to claim 18.

--23. **(New)** A method for detecting antibodies present in sera from patients with rheumatoid arthritis, comprising:

a) contacting a biological sample to be analyzed for the presence of said antibodies with a peptide of claim 1, and

c) detecting the immunological complex formed between said antibodies and said peptide.

~~24~~ 25. **(New)** The peptide of claim 7 which has the primary amino acid structure:
8 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 4).

25. **(New)** The peptide of claim 8, wherein the amino acids flanking the citrulline residue have a small volume.

26. **(New)** The peptide of claim 8 wherein the amino acids flanking the citrulline residue are selected from the group consisting of glycine, alanine, and serine.

27. **(New)**The peptide of claim 9 which comprises the amino acid sequence QDTIHGHPCSXXGCRPGY (SEQ ID NO: 12).--